REMARKS

Claims 1-29, as amended and new claims 32-57, are pending for the Examiner's review and consideration. Claims 30-31 are cancelled without prejudice to Applicants' rights to file one or more continuing applications directed to this or other unclaimed subject matter. Claims 1, 12 and 29 were amended to recite that the peptide concentration in the suspension is at least 25 mg/mL (Specification at ¶ [0016]). The following amendments are made to more clearly and distinctly recite the invention, and as such, are not intended to affect the scope of the claims. Claims 3-8, 10-11, 14-19, 21-22, and 24 were amended to replace "in which" to the clearer language wherein. Claim 25 was amended to clarify that it is the peptide that is at least partially in the form of microcrystals (Specification at ¶ [0018]).

New claims 32-44 are directed to the embodiment of the invention where the peptide is Ac—D—Nal—D—Cpa—D—Pal—Ser—Tyr—D—Hci—Leu—Ilys—Pro—D—Ala—NH_2 and the counter-ion is trifluoroacetate (Specification at ¶ [0008]). Similarly, new claims 45-57 are directed to the embodiment of the invention where the peptide is Ac—D—Nal—D—Cpa—D—Pal—Ser—Tyr—D—Hci—Leu—Ilys—Pro—D—Ala—NH_2 and the counter-ion is sulfate (Specification at ¶ [0008]). Claims 32 and 45 each recite a fluid, milky aqueous suspension of Ac—D—Nal—D—Cpa—D—Pal—Ser—Tyr—D—Hci—Leu—Ilys—Pro—D—Ala—NH_2·trifluoroacetate or Ac—D—Nal—D—Cpa—D—Pal—Ser—Tyr—D—Hci—Leu—Ilys—Pro—D—Ala—NH_2·sulfate (Specification at ¶ [0005]). Claims 33 and 46 are directed to suspensions that provide a sustained release of peptide in vivo (Specification at ¶ [0007]). Claims 34 and 47 relate to suspensions wherein the sustained release is over a period of two weeks (Specification at ¶ [0007]). Claims 35 and 48 are directed to suspensions wherein the salt is suspended in an aqueous medium at a concentration of equal to or greater than 25 mg/mL (Specification at ¶¶ [0009] and [0016]). Claims 36 and 49 relate to suspensions comprising an isotonic agent (Specification at ¶ 0016]). Claims 37 and 50 recite that the isotonic agent is mannitol (Specification at ¶ [0016]). Claims 38 and 51 relate to suspensions that comprise a pharmaceutically acceptable excipient (Specification at ¶ [0010]). Claims 39 and 52 are directed to microcrystals in the form of needles having a particle size of between 1 and 150 μm (Specification at ¶¶ [0009] and [0021]). Claims 40 and 53 relate to methods of preparing a suspension of the peptide salts by associating Ac—D—Nal—D—Cpa—D—Pal—Ser—Tyr—D—Hci—Leu—Ilys—Pro—D—Ala—NH_2 with either trifluoroacetate or sulfate to provide a fluid, milky suspension without formation of a gel (Specification at ¶ [0005]).

Claims 41 and 54 are directed to methods of preparing a lyophilized composition comprising lyophilizing the suspensions (Specification at ¶ [0010]). Claims 42 and 55 are directed to lyophilized compositions prepared by these methods (Specification at ¶ [0010]). Claims 43 and 56 relate to methods of preparing microcrystalline aqueous suspensions by adding water or buffer with mixing to lyophilized compositions (Specification at ¶ 0017). Lastly, claims 44 and 57 recite methods of preparing microcrystalline aqueous suspensions of a peptide salt by associating antarelix with either trifluoroacetate or sulfate to provide a fluid, milky microcrystalline suspension without formation of a gel, lyophilizing to form a lyophilized composition, and adding water or buffer with mixing (Specification at ¶ [0010]). Applicants note that antarelix and Teverelix® refer to the same peptide. No new matter has been added by way of these amendments and new claims, such that their entry at this time is warranted.

Claims 26-28 were rejected under 35 U.S.C.§ 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter (Office Action at page 2). In particular, the Examiner noted that there was insufficient antecedent basis for "the dried suspension" recited in claim 26 (*Id.*). Claim 26 has been amended to recite "a dried suspension" to clarify this language. Thus, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Claim 30 was rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,258,933 to Günther et al. ("Günther") (*Id.*). Günther is stated to disclose antarelix trifluoracetate and its amino acid sequence (*Id.* at page 3).

Günther discloses a one-step process for the resalting and purification of oligopeptides (Col. 2, lines 38-42). Günther further teaches that an oligopeptide in the form of its hydrochloride salt is resalted and purified, via liquid chromatography by means of an acetate-containing solvent, to yield practically chloride-free purified oligopeptide acetates (Col. 2, lines 49-54).

Claim 30 has been cancelled and has been replaced with new claims 37-44, which each recite microcrystalline aqueous suspensions of antarelix trifluoroacetate. Günther does not disclose or suggest such microcrystalline aqueous suspensions of the salt. Instead, Günther adds diisopropyl ether to antarelix that is dissolved in trifluoroacetic acid (Col. 6, lines 19-20). The salt obtained is thereafter suction filtered, washed with additional diisopropyl ether and dried in vacuo (Col. 6, lines 20-25). Günther's solution is not aqueous and does not contain a microcrystalline suspension. Thus, Günther fails to teach each and every recited feature.

Moreover, Günther discourages the use of the trifluoroacetate salts of peptides:

> It has now completely surprisingly but nevertheless advantageously been found that protected oligopeptides can also be de-protected with concentrated aqueous hydrochloric acid and that the salts of the oligopeptides formed therefrom contain a significantly lower proportion of by-products compared to the more conventional cleavage with the *less strong, anhydrous trifluoroacetic acid*, possibly mixed with organic solvents, or with the HBr/acetic acid system. (emphasis added, Col. 3, lines 10-20).

For these reasons, Applicants respectfully request that this rejection under 35 U.S.C. § 102(e) be reconsidered and withdrawn.

Claims 1-6, 9-17, 20-24, 26-29 and 31 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Publication No. 2002/0198146 to Damm et al. ("Damm") (Office Action at page 3). Damm is alleged to provide a method of synthesizing peptide salts (*Id.*). The method purportedly comprises adding acids, including benzenesulfonate and sulfate, to a peptide to form the corresponding salts in a cloudy suspension (*Id.*). The Office Action alleges that Damm teaches that preferred peptides are LHRH antagonists and that this includes antarelix, abarelix, azaline and cetrorelix (*Id.*). Moreover, Damm is alleged to teach that the suspension of the peptide salt in water is filled in an amount of 3.0 grams into 10 mL injection flasks, and that this results in a concentration of the peptide salt in the aqueous suspension of 300 mg/mL (*Id.*). Damm is further alleged to teach an aqueous suspension of the peptide salt that is administered parenterally; a dose of 30-150 mg; adjuvants, including mannitol, that may be added to the composition; and a lyophilizate of centrolix embonate, which is resuspended in water and administered parenterally (*Id.* at page 4).

Independent claims 1, 12 and 29 have been amended to recite that the concentration of the peptide in the suspension is <u>at least 25 mg/mL</u>. Applicants concede that Damm generally teaches a method for producing peptide salts that includes reacting a peptide with an acid to form the desired acid addition salt of the peptide. Damm does not, however, disclose or suggest use of the peptide or peptide salt in concentrations as high as 25 mg/mL. Instead, the concentrations of the peptide or salt disclosed in Damm range from 34.07 mg/2 mL to 30 mg/2 mL (Specification at ¶¶ [0025] and [0027]). These concentrations translate to about 17 mg/mL and 15 mg/mL, respectively, which is significantly lower than the <u>at least 25 mg/mL</u> concentration presently claimed. Moreover, the reaction solution of the peptide base and the acid "usually is clear" and then filtered sterile (Specification at ¶ [0015]). Thus,

Damm teaches clear solutions rather than cloudy, or milky microcrystalline suspensions as presently recited.

Contrary to the allegation in the Office Action, Damm does not disclose or even remotely suggest concentrations as high as 300 mg/mL. Damm states that 3.0 grams of the suspension is placed into 10 mL flasks (Specification at ¶ [0022]). Each injection flask contains 34.07 mg of the salt, corresponding to 30 mg of the peptide (Specification at ¶ [0025]). 2 mL of water is added to form the suspension (Specification at ¶¶ [0025] and [0027]).

Indeed, the likely reason for the low concentrations disclosed in Damm is the low solubility of the salts in water. Damm even states that his method of synthesizing peptide salts is directed "especially [to] peptide salts of low solubility" (Specification at ¶ [0001]). The only example disclosed is that for the preparation of cetrorelix embonate (Example 1). As proof of the insolubility of the embonate salt, when the solution of the embonate salt was evaporated off to form a suspension of about 1,931 grams, cooled to room temperature and diluted to 3,000 grams with water, another suspension was formed (Specification at ¶ [0022]). The fact that a suspension remains even after dilution with such a large amount of water shows that the embonate salt is sparingly soluble. Thus, Damm fails to teach milky solutions, much less milky suspensions as presently recited, and Damm also fails to teach concentrations of at least 25 mg/mL, as presently recited.

Moreover, Damm does not inherently disclose or suggest highly soluble salts. Damm teaches preparing its insoluble salts through an ion exchange process, which is completely different than the claimed methods and therefore provides a different salt product that is insoluble.

Furthermore, several issued patents, including U.S. Patent No. 5,776,885 to Orsolini et al. ("Orsolini"), disclose insoluble acid addition salts of polypeptides, such as pamoate (embonate), tannate and stearate salts (Col. 1, lines 53-60 and Example VI). These water insoluble salts are not crystalline or microcrystalline. Like Damm, the goal of Orsolini was to provide a sustained release of the peptide through a water insoluble salt, which would slowly release the active principle *in vivo*.

In contrast, the salts of the present invention are microcrystalline, as presently recited. These salts are water soluble, but are slow-releasing because they are injected as solid microcrystals that dissolve in an aqueous medium over time. Concentrations of at least 25 mg/mL of the peptide or salt are used in the present invention. In fact, amounts as high as 100 mg/mL can be used, and these suspensions can also contain other additives

(Specification at ¶ [0016]). Orsolini and Damm do not teach microcrystalline suspensions. The present invention, however, recites microcrystalline suspensions. Thus, independent claims 1, 12 and 29, as well as dependent claims 2-6, 9-11, 13-17, 20-24, 26-28 and 31 are not anticipated or even rendered obvious by Damm. Applicants have obviated this rejection under 35 U.S.C. § 102(e) and respectfully request that this rejection be reconsidered and withdrawn.

Claims 7-8, 18-19 and 25 were rejected under 35 U.S.C. § 103(a) as obvious over Damm as applied to claims 1-6, 9-17, 20-24, 26-29 and 31, and further in view of U.S. Patent No. 5,648,096 to Gander et al. ("Gander") (Office Action at page 5). The Office Action admits that Damm does not disclose somatostatin analogues or particle sizes (*Id.*). Gander is alleged to provide suspensions of active ingredients in micronized form and teach that the particles are smaller than 10 μm (*Id.*).

Gander relates to a process for the production of biodegradable microcapsules (Col. 1, lines 9-10). Sustained release of active materials can be achieved through incorporating an active material into a biodegradable release system (Col. 1, lines 34-35). These release systems can be produced in the form of microcapsules (Col. 1, lines 37-38).

As discussed above, Damm does not disclose or even suggest use of a peptide in concentrations as high as 25 mg/mL, as is presently claimed. Gander fails to remedy this deficiency. That is, Damm and Gander even when combined do not teach a concentration of peptide of at least 25 mg/mL and do not teach microcrystalline suspensions, and therefore, do not teach or suggest each and every feature of the claimed invention.

Moreover, one of ordinary skill in the art would have had no motivation to combine Damm with Gander. Damm provides a sustained release of a peptide through a water insoluble salt. Gander, on the other hand, provides a sustained release of an insoluble active material by further processing the active material into microcapsules (*See* Col. 4, lines 43-52 and Col. 5, lines 22-25). Damm does not need the additional step of encapsulation to provide for sustained release. Even if a motivation to combine these references existed, the combination teaches away from the claimed invention because they both teach insoluble salts while the claims presently recite at least 25 mg/mL of peptide in a microcrystalline aqueous suspension. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn because no *prima facie* case of obviousness has been made on the record.

Applicants now believe all claims to be in condition for entry and allowance. Should the Examiner not agree with this position, a telephone or personal interview is requested to resolve any remaining issues and expedite allowance of this application.

Respectfully submitted,

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Date

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